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Clinicopathological review of patients with and without multiple sclerosis treated by partial sensory rhizotomy for medically refractory trigeminal neuralgia: A 12-year retrospective study

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ABSTRACT

Background: Trigeminal nerve root entry zone demyelination has been implicated as a cause of trigeminal neuralgia (TN) in multiple sclerosis (MS) and patients with nerve root vascular compression. We have examined the relationship between pathology and treatment outcome in patients with and without MS, treated for intractable TN by partial sensory rhizotomy (PSR).
Methods: We reviewed the operative records, electron microscopic biopsy findings and post-operative satisfaction and pain scores of 23 MS and 47 non-MS patients who underwent PSR between 1992 and 2004.
Results: The MS and non-MS patients had similar ages of onset of TN, duration of symptoms, age at surgery and proportions with typical and atypical symptoms. Demyelination was present in 16 MS and 23 non-MS patients ($p = 0.129$), and a compressing vessel in 5 MS and 23 non-MS patients ($p = 0.039$). Of those with demyelination, vascular compression was documented in 3 MS and 15 non-MS patients ($p = 0.008$). Pain and satisfaction scores were similar in both groups. Recurrent TN was more commonly associated with a compressing vessel ($p = 0.019$).
Conclusions: TN is frequently associated with nerve root entry zone demyelination in MS and patients with nerve root vascular compression. The characteristics of the TN and response to PSR are similar in both groups. Persistent vascular compression increases the risk of recurrent TN after PSR.

1. Introduction

Previous studies have implicated demyelination in the proximal (CNS) part of the trigeminal sensory nerve root and ephaptic spread of excitation as a cause of trigeminal neuralgia (TN) in patients with multiple sclerosis (MS) and in so-called idiopathic TN associated with vascular compression of the trigeminal nerve root [1–5]. However, the documentation of this relationship was based on pathological assessment of only a small number of cases and there is no published information on the relationship between nerve root demyelination, vascular compression and clinical outcome. We have now reviewed the clinical presentations, intraoperative findings and treatment outcomes in a large series of MS and non-MS patients treated for intractable TN over a 12-year period, from whom partial sensory rhizotomy (PSR) specimens were examined by electron microscopy.

2. Methods

2.1. Patients

Between 1992 and 2004 we examined PSR specimens from 72 patients with TN who had not responded to medical treatment, radiofrequency lesioning or, in some cases, other ablative procedures excluding radiosurgery. These patients were a subset of a larger group of patients who had been treated neurosurgically over the same period for TN, most of them by microvascular decompression (MVD) of the trigeminal nerve root. The present series comprised 23 patients (17 female, 6 male) with TN due to multiple sclerosis (MS) and 47 patients (29 female, 18 male) who had idiopathic TN with no demonstrable or convincing compression of the nerve root, or who had not responded satisfactorily to microvascular decompression, or in whom despite neurovascular compression,

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safe decompression was either judged not to be feasible or could not performed to a satisfactory extent due to technical reasons. The biopsy findings in 6 of the patients with MS and 3 of the patients with neurovascular compression were reported previously [1,4,5]. For the present study we reviewed the medical records of all 70 of the patients in the two groups and analyzed the clinical information in relation to the biopsy findings. A further 2 patients whose trigeminal rhizotomy specimens we received for examination were excluded from the study as their medical records were not available for review.

2.2. Clinical information

Information retrieved from the medical records included the age of onset and duration of the TN; the side and divisions affected; whether or not the pain at baseline, prior to any intervention, was typical or atypical (presence of associated background constant dull ache or sensory loss) of TN; results of pre-operative magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA); the age at PSR; the intraoperative findings with respect to vascular compression of the nerve root (at either initial or subsequent operative exposure of the nerve, in those patients who had repeated surgery) and post-operative complications. Other recorded information included the length of post-operative follow-up; evidence of recurrence; post-operative patient satisfaction graded subjectively and ranging from excellent to poor and the pain score at the last follow up.

2.3. Biopsy

In all cases, a wedge-shaped fragment of tissue, which measured approximately 2–3 mm in maximum diameter, was excised from the trigeminal nerve root and immediately placed in 2.5% cacodylate-buffered glutaraldehyde. In patients with vascular compression of the root, the excised fragment was taken as close as safely possible to the region of maximum compression. In patients without vascular compression, tissue was excised from the caudal part of the trigeminal nerve root, close to the pons. After overnight fixation at 4 °C, the specimens were subdivided into smaller blocks, post-fixed in 1% osmium tetroxide and 7.5% magnesium uranyl acetate, and embedded in Spurr resin (Agar Scientific, Essex, UK). Semi-thin sections were stained with toluidine blue and ultrathin sections with lead citrate. Electron microscopy was performed on all of the biopsies. For the present study, the biopsies were subdivided into those that included a region of demyelination with or without evidence of remyelination, i.e. absence of CNS myelin around intact axons, as previously described [1,3–5], and those with no demyelination. A few biopsies showed focal axonal degeneration, usually in the PNS part of the biopsy and thought to relate to previous ablative procedures; these biopsies were not classified as showing demyelination.

2.4. Statistical analysis

Data were analyzed by independent-samples *t*-test, Fisher's exact test or Chi-squared test, as appropriate, with the help of GraphPad Prism version 4.02. Values of $p < 0.05$ were considered to be statistically significant.

3. Results

3.1. Pre-operative findings

The age of onset of TN in the MS and non-MS groups was similar. The mean age in patients with MS was 50.0 years (SD = 11.6, range 30–69) and in the non-MS group 50.3 years (SD = 12.3, range 20–70.5) ($p = 0.923$). Also similar was the duration of TN in the two groups (in MS patients, mean = 7.7 years, SD = 5.7, range 1–20; in non-MS patients, mean = 6.7 years, SD = 6.7, range 0.5–32; $p = 0.552$) and the age at PSR (in MS patients, mean = 57.7 years, SD = 9.7, range 40–77; in non-MS patients, mean = 57.1 years, SD = 13.2, range 22–78; $p = 0.828$). The neuralgia was right-sided in 14 MS patients and left-sided in 9. In none was the TN bilateral. In non-MS patients the distribution was more equal (right-sided in 23 and left-sided in 24) but the difference between the groups was not significant ($p = 0.447$). The proportions of patients who had typical and atypical neuralgia were similar in the two groups (typical in 16 and atypical in 7 MS patients; typical in 30 and atypical in 17 non-MS patients; $p = 0.790$). In almost all patients in both groups, the neuralgia involved 2nd and/or 3rd division(s) of the trigeminal nerve. In 3 patients with MS and 2 without MS, the 1st division was involved as well as the 2nd division, and in a single non-MS patient the neuralgia affected the 1st division only.

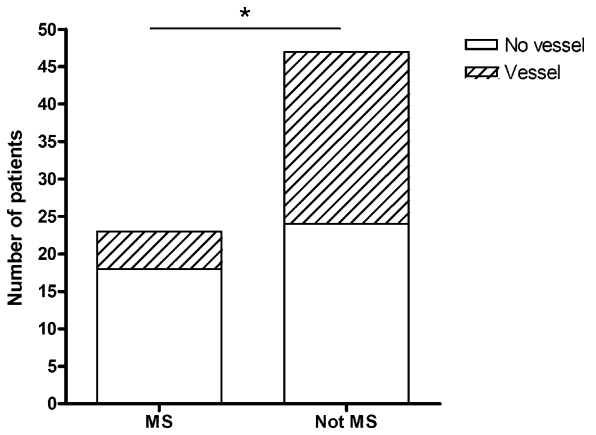

Fig. 1. Bar chart indicating the number of MS and non-MS patients in whom a compressing blood vessel was not (open bars) or was (cross-hatched bars) documented. A compressing vessel was documented in proportionately more of the non-MS patients ($p = 0.039$).

3.2. Intraoperative and pathological findings

Intraoperative examination revealed venous or arterial compression of the trigeminal nerve in the root entry zone in significantly fewer patients with than without MS. Vascular compression of the nerve root (Fig. 1) was found in 23 of the 47 patients who did not have MS (and was present on at least one occasion in patients who had repeat surgery), and in 5 of the 23 MS patients ($p = 0.039$). Subsequent pathological examination revealed a region of demyelination in the specimen of nerve root resected from 23 of the patients who did not have MS and 16 of those who did ($p = 0.129$).

In <20% of MS but >65% of non-MS cases, demyelination was associated with vascular compression ($p = 0.008$, Figs. 2 and 3). In the patients with MS, there was no demonstrable relationship between the presence or absence of a compressing vessel and the presence or absence of demyelination: of the 5 patients with a compressing vessel 3 had demyelination in the rhizotomy specimen and 2 did not; of the 18 patients without a compressing vessel 13 had demyelination and 5 did not ($p = 0.621$). However, there was a significant relationship between the presence of a compressing vessel and the presence of demyelination in the non-MS patients: of the 23 patients with a compressing vessel 15 had demyelination in the rhizotomy specimen and 8 did not; of the 24 without a compressing vessel 8 had demyelination and 16 did not ($p = 0.042$) (Fig. 4).

The presence or absence of demyelination bore no relationship to whether or not the TN was typical or atypical: of patients with

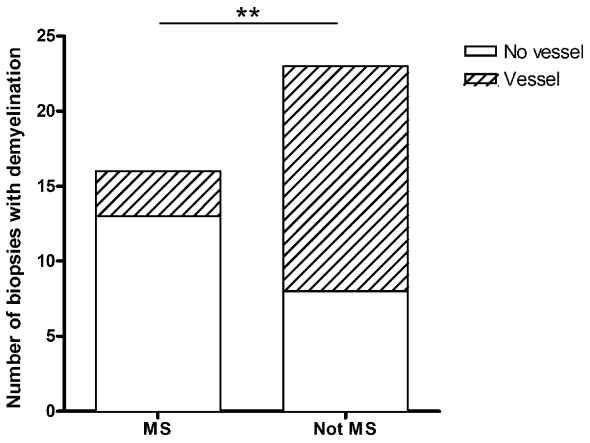

Fig. 2. Of the patients with nerve root demyelination, significantly fewer of the MS (<20%) than the non-MS patients (>65%) had a compressing vessel ($p < 0.008$).

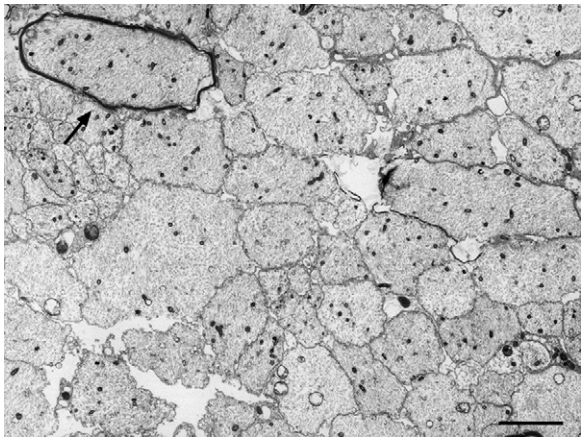

Fig. 3. Example of trigeminal nerve root demyelination in a patient with vascular compression of the nerve root. The field includes only a single myelinated fibre (arrow); the disproportionately thin myelin sheath in relation to the calibre of the axon suggests that the fibre has been remyelinated after previous demyelination. Elsewhere the biopsy consists of closely packed demyelinated axons. Bar = 5 μm.

demyelination 25 (11 with MS, 14 without MS) had typical TN and 14 (5 with MS and 9 without) had atypical TN; of patients without demyelination 21 (5 with MS and 16 without) had typical TN and 10 (2 with MS and 8 without) had atypical TN ($p > 0.7$ for both MS and non-MS cases).

3.3. Post-operative findings

The length of follow-up was shorter in the MS group (mean = 1003 days, median = 883 days, SD = 658 days, range 71–2430 days) than the non-MS group (mean = 1450 days, median = 1162 days, SD = 1181 days, range 3–4101 days) ($p = 0.004$), which should be borne in mind in interpreting comparisons in outcome between the groups.

The follow-up scores for pain and patient satisfaction were similar in the patients with and without MS. 20 of the 23 MS patients reported only mild (2) or no pain (18) at last follow-up after PSR, 1 had moderate pain and 2 continued to complain of severe pain. 44 of the 47 non-MS patients reported only mild (7) or no pain (37) at last follow-up after PSR and 3 continued to complain of severe pain ($p = 0.454$). Patient satisfaction was good to excellent in 19 and poor in 4 of those with MS, and good to excellent in 38, moderate in 3 and poor in 6 of those without MS ($p = 0.156$). Neither the pain nor the patient satisfaction score (Fig. 5) was related to the presence or absence of a compressing vessel at operation ($p = 0.133$ for pain score, $p = 0.325$ for patient satisfaction score) although it was noteworthy that most of the patients with persistent severe pain (4 out of 5) had a compressing vessel. Neither score was related to the presence or absence of demyelination in the rhizotomy specimen ($p = 0.220$ for pain score, $p = 0.391$ for patient satisfaction score). Recurrent TN was more common in patients with a compressing vessel ($p = 0.019$) (Fig. 6).

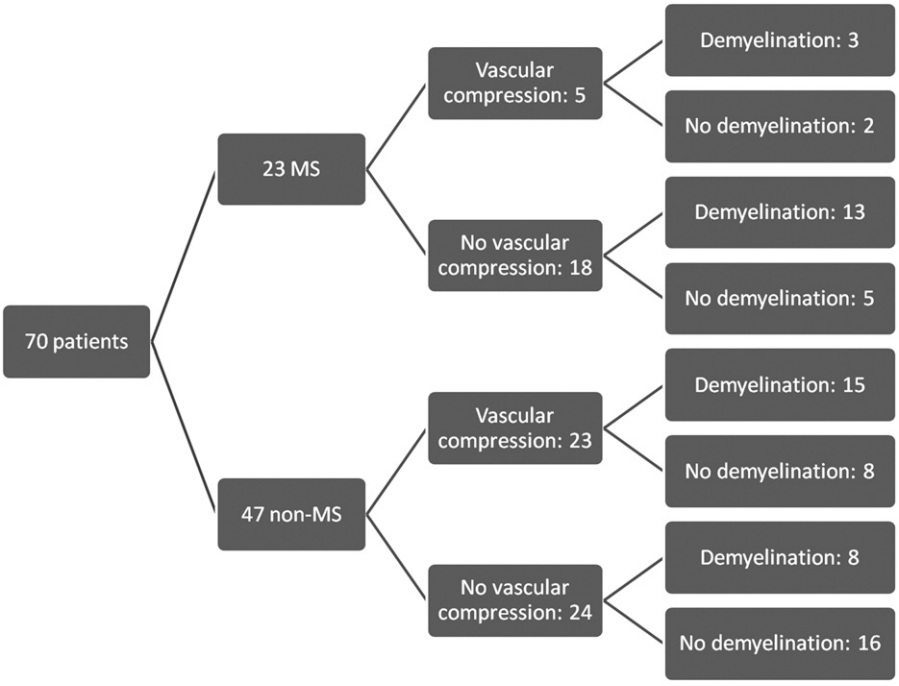

Fig. 4. Diagrammatic summary of the relationship between presence or absence of MS, presence or absence of vascular compression, and presence or absence of demyelination on pathological examination in the TN patients studied.

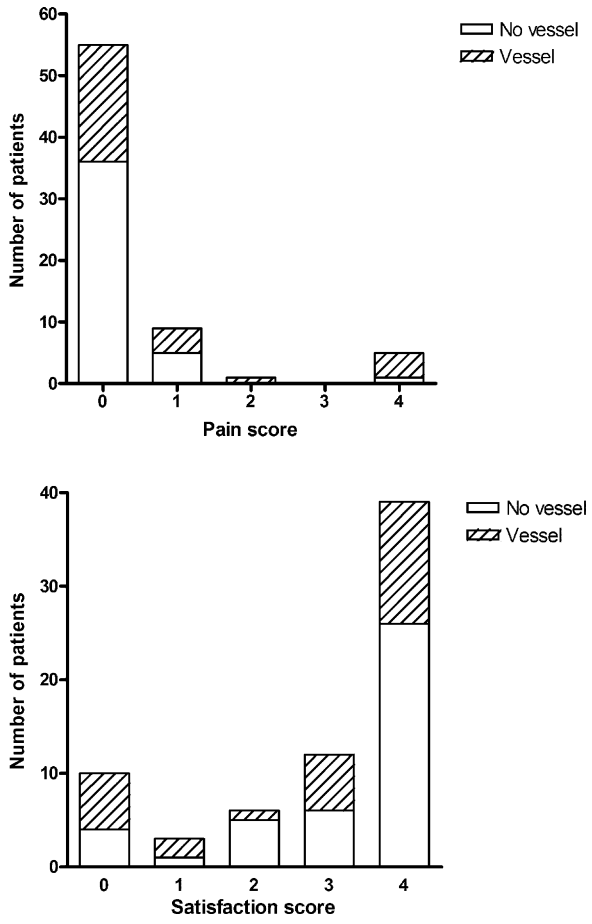

Fig. 5. Most patients had a good or excellent outcome after PSR, as indicated by low pain scores (upper panel) and high satisfaction scores (lower panel). Neither score was significantly associated with the presence of a compressing vessel, although this was documented in 4 of the 5 patients with persistent severe pain after PSR.

The number of patients reporting facial numbness in the affected trigeminal nerve distribution was 58 (MS = 22, non-MS = 36). 12 patients experienced depression of the corneal reflex, whilst one patient with MS reported symptoms of anaesthesia dolorosa.

4. Discussion

Our present findings confirm the association of nerve root entry zone demyelination with TN, in both MS and patients with nerve root vascular compression, in much the largest series of TN patients in which the trigeminal nerve root has been examined by electron microscopy. Demyelination was present in PSR specimens from most MS and non-MS patients, although vascular compression was more likely to be present in the non-MS patients. However, demyelination was significantly associated with a compressing vessel in the non-MS group only. The clinical characteristics of the TN were similar in the MS and non-MS patients and both groups responded well to PSR with minimal risk of anaesthesia dolorosa.

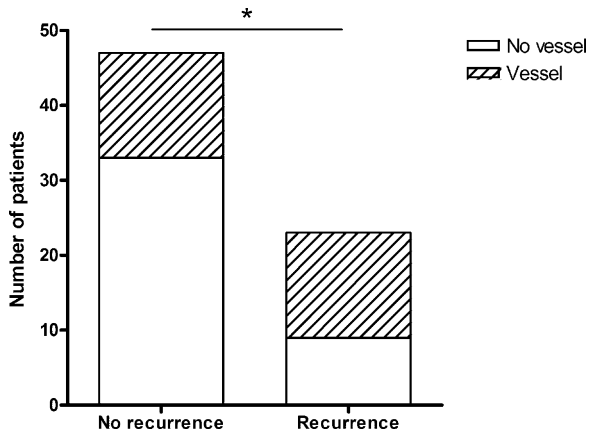

Fig. 6. Recurrent TN was significantly more common in patients with a compressing vessel ($p = 0.019$).

Most series have reported that TN in MS is more often bilateral and develops at an earlier age than in sporadic TN [2,6,7]. In our study, the age of onset of TN in the MS and non-MS groups was similar and in none of the patients was the TN bilateral. Furthermore the duration of TN and the proportion of patients with typical and atypical neuralgia were similar in both groups; in effect therefore the two groups were clinically indistinguishable apart perhaps from evidence of other neurological deficits associated with MS. In almost all patients, the neuralgia involved maxillary and/or mandibular divisions of the trigeminal nerve. The greater frequency of involvement of these divisions is probably due to the anatomical relationship between proximal trigeminal nerve root and blood vessels implicated in neuralgia.

Vascular compression was more common in non-MS than MS cases. This was expected. However, it is noteworthy that 5 of the 23 MS patients had evidence of vascular compression. In some series up to half of MS patients with TN had evidence of vascular compression and the neuralgia responded well to MVD [8–11]. We previously discussed this in a case series of five patients with multiple sclerosis and TN [12]. However, in our current series, although there was a significant relationship between the presence of a compressing vessel and demyelination in non-MS patients, this relationship was not significant for MS patients. The present findings are in keeping with the concept that MS-related TN is usually caused by inflammatory demyelination rather than vascular compression, although in some cases the two processes may act in concert. In our previous studies of TN associated with vascular compression we observed demyelination in the trigeminal nerve root entry zone root (within the central nervous system) but in most cases close to the junction with the distal (peripheral nervous system) part of the root. Within the region of demyelination many fibres were closely apposed, with an absence of intervening glial processes [1,3,5]. We demonstrated similar pathological findings in MS patients with TN [4], in whom the proximal part of TN nerve root is demyelinated, usually without co-existing neurovascular compression. However, the pathological findings usually differed from those in TN due to vascular compression in that the region of demyelination showed evidence of a chronic inflammatory process, with perivascular lymphocytes and lipid-laden macrophages and numerous astrocytic processes [4].

The pathophysiology of TN has been extensively debated, with the pain thought to be a consequence of hyperactivity or abnormal discharges arising from the gasserian ganglion, 'injured' nerve root and the trigeminal nucleus within the brain stem [13–17]. Demyelinated axons can predispose to generation of ectopic impulses as demonstrated in experimental studies [18–20]. Irrespective of the mechanism of demyelination, the close apposition of demyelinated axons should encourage ephaptic transmission of nerve impulses, thereby facilitating propagation and spread of impulses as demonstrated previously between immediately adjacent non-myelinated axons in experimental studies [18,21]. The present series included two, relatively small groups of patients in whom the pathogenesis of the TN remains enigmatic. The first group comprised patients in whom we found neither focal vascular compression nor evidence of demyelination. In some of these cases the TN may have been caused by focal nerve root or nerve compression or cryptic demyelination that was not visualized at craniotomy or on neuroimaging

or be related to arachnoid tethering or aberrant cerebrospinal fluid flow. Sampling of the nerve root for histology was limited by the small size of the biopsy sample, approximately 2–3 mm in diameter. The second group comprised patients with nerve root demyelination in the absence of vascular compression or other evidence of MS. It is possible that a proportion of non-MS patients with TN in the absence of vascular compression or demyelination subsequently develop MS, although none of our patients with unexplained demyelination had preoperative clinical or MRI evidence of MS, or developed radiological or clinical manifestations of MS during follow up.

Although the length of follow up was shorter in the MS group, the pain and patient satisfaction scores after PSR were similar in both groups, and neither score was related to the presence or absence of a compressing vessel or demyelination. The outcome after PSR was excellent or good in most patients, including in those with MS. The site at which the PSR is usually performed corresponds to the inferior aspect of the trigeminal nerve root entry zone, which carries most of the pain fibres that are destined to enter the spinal tract of the trigeminal nucleus and pass caudally within the medulla and upper spinal cord. The frequent involvement of the inferior part of the nerve root entry zone in TN is not thought to be due to a predilection of this region to undergo demyelination but rather to reflect the close proximity of fibres subserving pain to those subserving light touch, facilitating ephaptic communication between the two types of nerve fibre in presence of demyelination [3]. However, a PSR in this region should lead to symptom relief even in the absence of demyelination. Recurrence of TN after PSR was uncommon in our series and presumably indicated ongoing ephaptic communication between light touch and preserved pain fibres away from the site of surgery, particularly in the context of continued vascular compression of the nerve root.

There were some unavoidable limitations to our study, partly related to its retrospective nature and partly to the fact that PSR is usually used only after the failure of other treatments for TN. The present series comprised a therapeutically challenging group of patients, not necessarily representative of TN patients in general: probably older and, after the failure of a succession of other treatments, perhaps less likely to be dissatisfied with residual numbness or incomplete resolution of symptoms. The prior ablative procedures may also have influenced the pathological findings in some cases, although in analyzing the relationships between nerve root demyelination, vascular compression and TN, we took the conservative approach of including only demyelination that was not associated with axonal degeneration. Potential discrepancies relating to the difficulties of interpreting the relationship between the clinical and pathological findings in individual cases were also mitigated by the large number of patients included in this study—much the largest series of TN patients for whom pathological data are available, based on detailed electron microscopic examination of optimally preserved biopsy tissue.

In conclusion, these findings help to establish the role of demyelination in the inferior part of the trigeminal nerve root entry zone as the cause of TN in most patients with MS and in 'idiopathic' TN associated with vascular compression of the nerve root. The outcome after PSR is generally good or excellent in both groups of patients and is not predictable on the basis of presence or absence of detectable vascular compression or demyelination, although recurrence is more likely in patients with continued vascular compression.

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